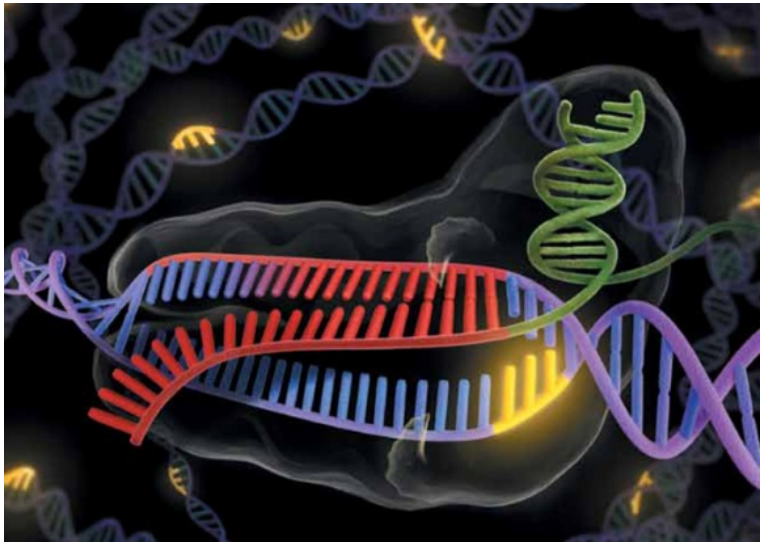
U.S. FOOD & DRUG ADMINISTRATION

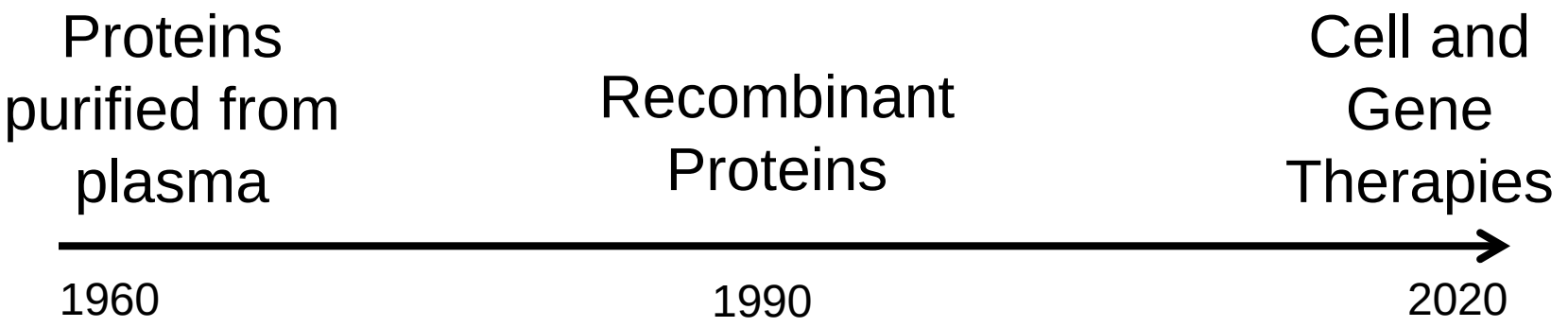
Gene Editing: CBER's Perspective



FDA Science Board Meeting

November 15, 2016

Evolution of CBER's Products



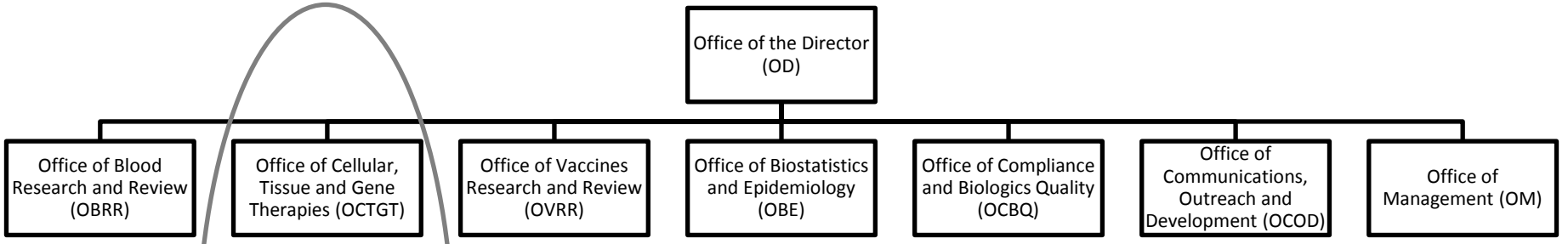
Example:

Factor VIII Concentrate (licensed)

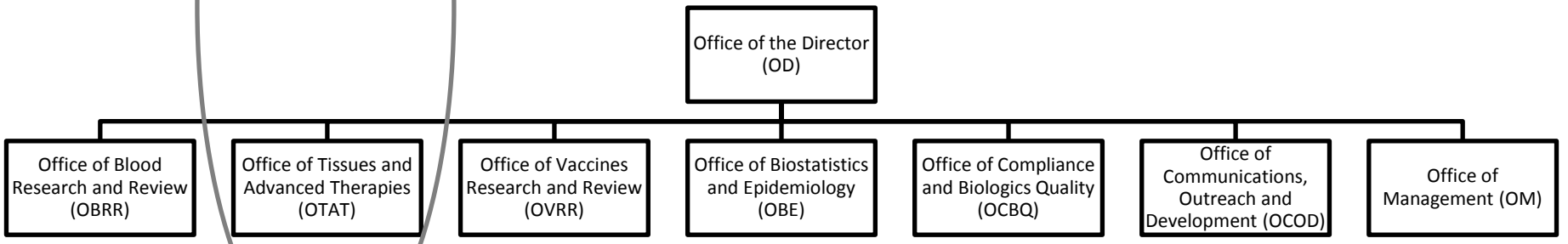
Recombinant Factor VIII (licensed)

Factor VIII Gene Therapy (in development)

Prior to Reorganization



Following Reorganization



Effective Date: October 16, 2016

Preparing for the Future at CBER

- Three new PI's recruited to address emerging scientific needs relevant to our regulated products, including gene editing, gene-modified T cells, and tissue engineering
- Participation in public meetings and workshops on gene editing
- Participation in the Recombinant DNA Advisory Committee Process with NIH
  - Non-voting member

Continued FDA Education

FDA Co-Sponsored Study

- National Academies of Sciences, Engineering, and Medicine Consensus Study on human gene editing: scientific, medical, and ethical considerations
- Will provide a framework based on fundamental, underlying principles that may be adapted and adopted by any nation that is considering the development of guidelines

Gene Editing Technology

- DNA inserted, deleted, or replaced in the genome of an organism using engineered nucleases (“molecular scissors”)
- Nucleases create site-specific double strand breaks (DSBs) at desired locations in the genome and the breaks are repaired through non-homologous end-joining (NHEJ) or homology directed repair (HDR) resulting in targeted mutations (edits)

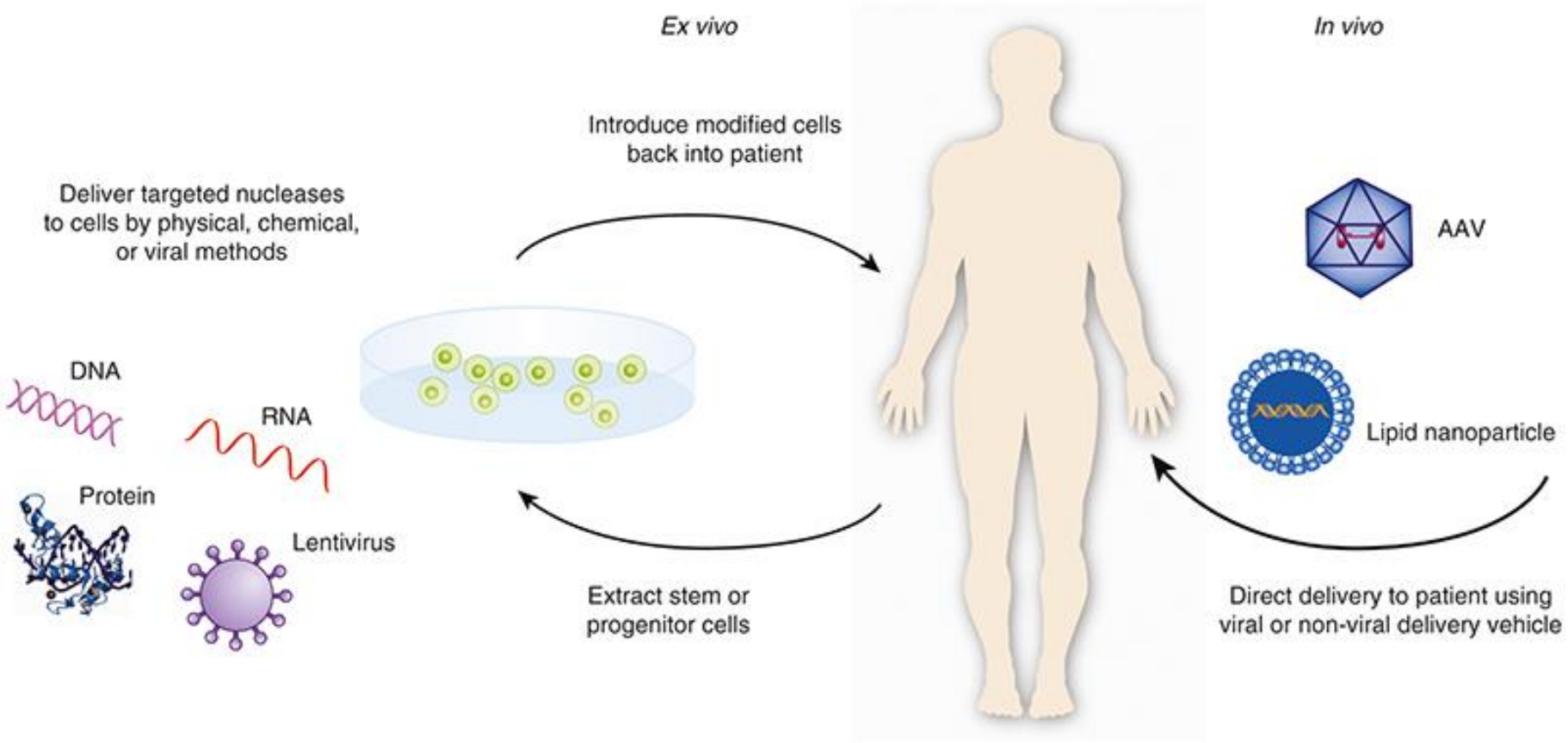
Nuclease for Gene Editing

- Zinc Finger Nucleases (ZFNs)
- Transcription Activator-Like Effector Nucleases (TALENs)
- Engineered Meganucleases
- Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas9)

Potential for Gene Editing

- Possible to modify somatic cell or germline genomes through relatively efficient targeted genetic modification, inactivating, inserting or changing genes
- FDA regulates somatic and germline gene modifications used as therapeutics in humans
  - Includes modification of cells prior to administration and gene therapy vectors
  - Somatic cell versus germline editing is currently relevant in humans

Ex vivo or *In vivo* Gene Editing



Scientific Considerations

Desirable

- Efficient delivery
- On target gene modification
- Targeted expression
- Long lasting expression
  - Depends on indication

Undesirable

- Immune response to vector or transgene
- Off target editing
- Off target expression
- Insertional mutagenesis

Other Considerations

- Potential germline transmission

Regulatory Considerations

- Nature of editing
  - Inactivation, insertion, modification
- Safety considerations
  - Percentage of cleavage at on- and off-target sites
  - Evaluation of the profile of insertions and deletions and types of mutations generated
- Science-based approach to regulation
- Benefit-risk analysis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